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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

| EXAMINER | |
|---|---|
| CANELLA, KAREN A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/837,138 | PETRINI ET AL. | |
| | Examiner | Art Unit | |
| | Karen A Canella | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *5,6,16-18 and 20-27* is/are pending in the application.

4a) Of the above claim(s) *16-18 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,22,26 and 27* is/are rejected.

7)☒ Claim(s) *20 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 5, 6, 16-18 and 20-27 are pending. Claims 16-18 and 23-25, drawn to non-elected inventions, are withdrawn from consideration. Claims 5, 6, 20-22, 26 and 27 are examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claims 5, 6, 22, 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for full length DNA repair proteins that bind to Mel1/Rad50, does not reasonably provide enablement for biological fragments thereof having DNA repair activity which bind to Mel1/Rad50. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 5 and 6 are drawn in part to a method reliant upon a biologically active fragment of a DNA repair polypeptide.

The specification merely contemplates that "biologically active fragments" are part of the claimed invention, not instructions limiting the type of biological activity, guidance with respect to specific protein domains nor have any working examples have been set forth.

The claims are drawn in part to methods of altering the amount of a DNA repair polypeptide in a cell by the expression of an isolated nucleic acid encoding, or antisense to, a biologically active fragment of a DNA repair polypeptide having a molecular weight of about 95 kDa. and which binds the Mrel1/Rad50 complex and which exhibits DNA repair activity It is noted that the specification does not teach a discreet enzymatic function for p95 and the only DNA repair activity which can be attributed to p95 is its presence in the mel1/Rad50 complex. The art teaches that the function of a single DNA repair protein is complex as it interacts with numerous cellular proteins. The specification teaches that the p95 of the instant invention is part of a complex comprising Mel1 and Rad50: The specification teaches that Nijmegen breakage syndrome patients possess a mutated NBS1 gene and cells taken from said patients exhibit impaired double strand break repair after exposure to ionizing radiation. The prior art (Dolganov

et al, Molecular and Cellular biology, 1996, Vol 16, pp. 4832-4841) and the instant specification teach that Mel1 and Rad50 associate with the instant p95 protein and two additional proteins of 200 kD and 350 kD. The specification does not teach a fragment of the p95 protein which could maintain the association with Mel1/Rad50/p200/p350 and it is unreasonable to assume that a fragment of p95 will be able to interact with the other members of the complex. There are no teaching in the specification to indicate that less than the full length of the p95 protein would be sufficient to maintain double strand break repair. The specification fails to teach fragments of the p95 polypeptide which retain a specific "DNA repair activity". Given these lack of teachings and the unreliability of the art with respect to the complexity of interactions between DNA repair polypeptides and other cellular proteins, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to make and use the broadly claimed invention.

Claims 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. the instant claims are drawn to host cells prepared by the instant method. The claims are not drawn to isolated host cells, thus, when given the broadest reasonable interpretation, read on host cells comprised within a living organism such as a transgenic animal or a human gene therapy patient. It is noted that the specification contemplates gene therapy on page 8, line 26 to page 9, line 6, and transgenic animals on page 9, lines 7-27. The specification is not enabling for host cells comprised within either the human patient or the transgenic animal fro the reasons set forth below.

(A)As drawn to gene therapy.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver

genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ( "Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the

expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B) as drawn to a transgenic animal

The specification states on pages 52-54 that genetically engineered host cells can be used to produce transgenic non-human animals. The specification does not provide guidance in the making of a transgenic animal comprising the instant recombinant polynucleotides or transformed cells. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. The vectors to be used for directing the expression of transgenes in a given tissue or in all tissues must contain the appropriate regulatory regions (Houdebine, Journal of Biotechnology, 1994, Vol. 34, pp. 269-287), see bridging pages 272-273) and expression is heavily dependent on the site of integration in the host genome, and the site of integration is presently unpredictable (Houdebine, page 277, column 1). Therefore, it is concluded that one of skill in the art would undergo undue experimentation in order to make the instant recombinant polynucleotides and cells within a transgenic animal.

Amendment of the claims to recite both "isolated vector" and "isolated host cell" would overcome this rejection.

The rejection of claims 5, 22, 26 and 27 under 35 U.S.C. 102(b) as being anticipated by Kowalski (WO 98/07030) as evidenced by Nickoloff and Hoekstra (DNA Damage and Repair, (monograph) Vol. 2, 1998, pages 348-349) is withdrawn in light of applicants amendments.

The rejection of claims 6 and 22 under 35 U.S.C. 102(b) as being anticipated by Housman et al (WO 98/41648) as evidenced by Nickoloff and Hoekstra (DNA Damage and

Repair, (monograph) Vol. 2, 1998, pages 348-349) is withdrawn in light of applicants amendments.

The rejection of claims 5 and 26 under 35 U.S.C. 102(e) as being anticipated by Camonis et al (U.S. 6,479,237) as evidenced by Nickoloff and Hoekstra (DNA Damage and Repair, (monograph) Vol. 2, 1998, pages 348-349) is withdrawn in light of applicants amendments.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure is Concannon et al (US 6,458,534, priority to May 27, 1998).

Claims 20 and 21 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth in Paper No. 17 are withdrawn.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/23/03

Karen A. Canella